

## REMARKS/ARGUMENTS

The instant invention concerns novel methods for the synthesis of oligonucleotides. The instant invention overcomes deficiencies in the synthesis art by allowing high yield coupling of phosphoramidite synthons to an oligomer chain that contains at least one unprotected phosphoryl protecting group (see page 5, lines 12-22). An important component in the instant method is the use of certain neutralizing agents in the synthetic process (page 6, lines 1-18).

Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, and 92-104 are pending. Claims 11-15, 36-40, 99, 100, and 103 are objected to as depending from rejected claims. These latter claims are amended so that they are in independent form. In addition, as discussed below, claims 48 and 98 are amended. Claims 7-10, 16-20, 22-35, 41-46, 53-55, 61-65, 67-80, 86-91, 102 and 105 are canceled without prejudice to their resubmission in a divisional application.

Claims 48-52, 56-60, 66, 81-85, 92-95, and 104 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The use of the term 2'-substituent in claim 48 is alleged to not apprise one of ordinary skill in the art as to the meets and bounds of the invention. Applicants assert, however, that one skilled in the art clearly understands the meaning of this term. Furthermore, the disclosure at page 29, line 13 to page 31, line 5 is sufficient for one to understand the scope of this term of art. In regard to the use of variables  $R_4$  and  $R_5$  in claim 48, this rejection is moot in view of the amendment to claim 48.

Claims 1-6, 21, 47-52, 66, 92-97, and 104 are rejected as allegedly obvious under 35 U.S.C. § 103(a) over Caruthers et al., Proceedings of the 2<sup>nd</sup> International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (the Caruthers reference) in combination with Beaueage et al, Tetrahedron 1992, 48, 2223-2311 (the Beaueage reference). The instantly claimed process differs significantly from that of the cited art. Claim 1, for example, is directed to a process where the support bound oligomer has at least one unprotected internucleoside linkage selected from the group consisting of phosphate linkages,

phosphorothioate linkages, and phosphorodithioate linkages. The process disclosed by Caruthers utilizes protected phosphate linkages which, as discussed on page 4, line 15 to page 5, line 22 of the filed specification, cause disadvantages versus the instantly claimed procedures. The Beaueage reference does not cure this defect. Thus, even if one were motivated to combine the teachings of the Beaueage reference with the Caruthers reference, a point that applicants do not concede, one would not arrive at any claimed invention. The above argument applies equally to 2-6, 21, 47-52, 66, 92-97, and 104 which also stand rejected by the same arguments. As such, Applicants respectfully submit that the rejection is improper and should be withdrawn.

Claims 98, 101, and 102 stand rejected as allegedly obvious over the Caruthers reference in combination with the Beaueage reference. The Beaueage reference only contains certain disclosures concerning the use of the N,N-diisopropylammonium salt of 1H-tetrazole. In view of the amendment to claim 98 which removes tetraalkylammonium salts from the claim, Applicants believe that the rejection is moot for this claim. Claim 101 is rewritten in independent form. This claim concerns compositions where the oligomer contains at least one linkage that is not protected. As discussed above, this differs from the teaching of the Caruthers reference and the Beaueage reference. Claim 102 is canceled as redundant versus claim 101. In view of these amendments and arguments, Applicants submit that the claims are allowable versus the cited art.

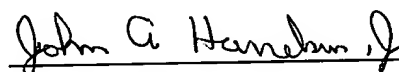
**DOCKET NO.: ISIS-4682**  
**Application No.: 09/775,967**  
**Office Action Dated: June 11, 2003**

**PATENT**

Applicants submit that all of the claims presently before the Examiner patentably define the invention over the prior art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,

Date: September 4, 2003



John A. Harrelson, Jr.  
Registration No. 42,637

Woodcock Washburn LLP  
One Liberty Place - 46<sup>th</sup> Floor  
Philadelphia, PA 19103  
Telephone: (215) 568-3100  
Facsimile: (215) 568-3439